FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Hilton Hotel, Silver Spring, Maryland
January 13, 2010

Questions to the Advisory Committee

The committee will discuss new drug application (NDA) 22-562, CARBAGLU (carglumic acid) Tablets, Orphan Europe, S.A.R.L. The proposed indication of Carbaglu in this application is for the specific treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency).

EFFICACY

1. The legal effectiveness requirement for drug approval is "substantial evidence," defined as "evidence consisting of adequate and well controlled investigations, including clinical investigations, on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports or is represented to have." In some cases, substantial evidence may be considered to be "data from one adequate and well-controlled clinical investigation and confirmatory evidence." (See Section II. A. of the *Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* for further discussion of the effectiveness requirement and how it should be applied.)

Do you consider that the clinical data included in the Carbaglu application for treatment of hyperammonemia in NAGS deficiency provided substantial evidence of efficacy?

Vote: Yes/No/Abstain

For those who answer "Yes" to Question 1:

2. Which clinical data provide substantial evidence?

3. Do the data support the effectiveness of Carbaglu for treatment of **acute** hyperammonemia in NAGS deficiency?

4. If so, do the data support labeling of use of Carbaglu without use of other adjunctive ammonia lowering therapies for treatment of **acute** hyperammonemia in NAGS deficiency?

5. Do the data support the proposed starting dose of Carbaglu (100 – 250 mg/kg/day in divided doses)?

6. Do the data support the effectiveness of Carbaglu for **chronic** treatment of hyperammonemia?

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7. If so, do the data support labeling of use of Carbaglu without use of other adjunctive ammonia lowering therapies for **chronic** treatment of hyperammonemia in NAGS deficiency?

8. Do the data support a maintenance dose of Carbaglu that can be included in product labeling?

9. Are there any additional analyses or studies that should be conducted?

For those who answer "No" to Question 1:

10. What are the deficiencies in the clinical data that make you consider the evidence to be less than substantial?

11. Are there additional analyses of the existing clinical data that could be performed that might affect your assessment?

12. Are there additional clinical studies of Carbaglu that you recommend be conducted prior to marketing approval to address the deficiencies you identified?

SAFETY

13. Has the safety of Carbaglu at the proposed dose in patients with hyperammonemia in NAGS deficiency been adequately assessed?
Vote: Yes/No/Abstain

14. Is the safety of Carbaglu at the proposed dose acceptable in hyperammonemia in NAGS deficiency?
Vote: Yes/No/Abstain

RISK/BENEFIT ASSESSMENT

15. In light of the safety and efficacy data presented in this application, does the risk/benefit profile of Carbaglu support its approval for treatment of hyperammonemia in NAGS deficiency?
Vote: Yes/No/Abstain